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FULL PAPER

SARS-CoV-2 versus Flu: ECMO-associated bloodstream infections

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SUMMARY

SARS-CoV-2 and flu may lead to severe acute respiratory distress syndrome (ARDS) requiring extracorporeal membrane oxygenation (ECMO). The aim of the present study is to compare the incidence of bloodstream infections (BSIs) and outcome in patients with flu and SARS-CoV-2 infection hospitalized in ICU and undergoing ECMO. This study is a retrospective analysis of the San Matteo COVID-19 Registry (SMACORE) cohort. The study was conducted from January 2018 to April 2020. Demographic data and microbiological data were recorded during hospitalization. BSIs occurring during ECMO were analyzed. Eighteen patients treated with ECMO, 22 subjects with SARS-CoV-2 infection and 7 with flu, median age 61years for SARS-CoV-2 and 50 for flu (p=NS). Median ECMO duration was similar in the two pathologies. Median time to bloodstream infection from ECMO initiation was similar. Bloodstream infection incidence rate was 2.65 per 100 patients/days for flu and 2.2 per 100 patients/days for SARS-CoV-2. Global infection rate was 5 per 100 patients/days for SARS-CoV-2 patients and 5.3 per 100 patients/days for flu. Mortality during ECMO was 40.9% (5 out of 22 patients) for SARS-CoV-2 infection while none died among flu patients. ECMO-associated mortality was higher in SARS-CoV-2 infection compared with flu infection.

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INTRODUCTION

Both seasonal flu and SARS-CoV-2 viruses can cause interstitial pneumonia that can lead to severe acute respiratory distress syndrome (ARDS), a type of acute inflammatory lung injury associated with increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue (ARDS Definition Task Force *et al.*, 2012) that may require intensive care assistance and in some cases entail extracorporeal membrane oxygenation (ECMO). Nosocomial infections are complications occurring in patients supported by ECMO, with reported rates ranging from 8% to 64% (Allou *et al.*, 2019), and are associated with worse outcome, including in-hospital mortality caused by septic shock. The most frequent nosocomial infections in patients supported by ECMO are ventilator-associated pneumonia (VAP) and bloodstream infection (BSI) (Allou *et al.*, 2019). Marcus and coauthors reported a higher incidence of infections in patients on ECMO for SARS-CoV-2 infection compared with patients on ECMO for flu infection; a possible explanation for this observation was the use of steroids in SARS-CoV-2 infection and high patient volumes, which strained healthcare systems (Marcus *et al.*, 2021). The aim of this study is to compare incidence, microbial etiology, resistance patterns and risk factors of BSIs and VAPs and outcome in patients with flu and SARS-CoV-2 infection, hospitalized in ICU and undergoing ECMO for respiratory failure.

Key words:
SARS-CoV-2, flu, ECMO, bloodstream infections

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MATERIALS AND METHODS

Data collection and selection of patients

This study is a retrospective analysis conducted among patients of the SMACORE Cohort. The SMACORE study was approved by the local Institutional Review Board, and includes patients with confirmed diagnosis of SARS-CoV-2 infection referred to our Fondazione IRCSS Policlinico San Matteo in Pavia. Patients with a confirmed diagnosis of flu infection who were treated with ECMO in the last three years

were also retrospectively analyzed. The SMACORE database includes demographic, clinical (symptoms at admission and comorbidities), laboratory data, treatment and outcome (admission to ICU, death, discharge) (Zuccaro *et al.*, 2021). The study was conducted from January 2018 to May 2021 on patients hospitalized in the Intensive Care Unit (ICU) of our hospital. All patients with a confirmed diagnosis of flu or SARS-CoV-2 infection who underwent ECMO were included. Data on bronchoalveolar lavage (BAL) and blood culture results collected during the ECMO period were analyzed.

Definition of infection

All patients with SARS-CoV-2 or flu infection tested positive for viral RNA from respiratory samples determined by specific real-time reverse transcriptase-polymerase chain reaction (RT-PCR).

Microbiology

Blood samples were cultured in BD BACTEC culture aerobic/anaerobic vials and were incubated in the BACTEC 9240 or FX automated blood culture system (Becton Dickinson and Company, Franklin Lakes, New Jersey, United States) according to the manufacturer's instructions. Positive blood cultures were subjected to Gram-staining and were sub-cultured as required by internal laboratory protocol.

All the respiratory specimens were plated by Automatic Streaking WASP® (Copan, Brescia, Italy) according to the manufacturer's recommendations: 10 µl of samples were streaked on chocolate agar +PolyViteX, Columbia agar +5% sheep's blood, Mannitol Salt agar, MacConkey agar, and CHROMID Candida agar (Biomerieux, Marcy l'Etoile, France); 90 µl of samples were streaked on Sabouraud Gentamicin Chloramphenicol agar (Biomerieux, Marcy l'Etoile, France). Cultures on chocolate agar + PolyViteX were incubated in 5% CO_2 at 36 ±1°C, while the other cultures were incubated aerobically at 36±1 °C. The culture plates for bacteria were read at 24 h and held for 2 days before reporting as negative, while cultures for yeasts and filamentous fungi were read and held for 5 days.

The bacterial and yeast isolates both in blood and respiratory samples were identified through matrix-as-

Table 1 - *Patient characteristics. Data are presented as percentage (absolute number) and median (interquartile ranges).*

	FLU	*SARS-CoV-2*	*p*
Number of patients	7	22	
Male % (n)	57.1 (4)	90.9 (20)	0.04
Median age	49.71 (41.0-59.0)	61.0 (55-68)	0.02
Major comorbidities % (n)			
Diabetes	28.6 (2)	18.2 (4)	ns
Hypertension	42.9 (3)	36.4 (8)	0.09
Obesity	28.6 (2)	13.6 (3)	-
Heart disease	14.3 (1)	13.6 (3)	-
Tumor	14.3 (1)	4.5 (1)	-
Lung disease	42.9 (3)	4.5 (1)	0.01
Immunosuppression	0 (0)	4.5 (1)	-
Renal replacement therapy % (n)	42.8 (3)	45.4 (10)	ns
Duration ECMO (median)	12.0 (8.5-16.0)	12.5 (6.2-21.2)	0.9
Mortality in ECMO % (n)	0 (0)	40.9 (9)	0.06
Hospital associated mortality % (n)	14.3 (1)	50 (11)	0.09
BSI			
BSI during ECMO % (n)	42.9 (3)	40.9 (9)	0.90
Time between starting ECMO and BSI (median (Q1-Q3))	7 (6.5-10.5)	5.5 (4.2-8.0)	-
VAP			
VAP during ECMO % (n)	57.1 (4)	59.1 (13)	0.09
Duration mechanical ventilation (median)	26 (22-29)	34 (20.7-41.7)	-
Time between intubation and VAP (days)	9.5 (5.0-14.0)	10.5 (5.0-17.7)	-
Virus detection on BAL for patient % (n)	85.7 (6)	81.8 (18)	-
Isolation of virus % (n)	100 (12)	63.6 (14)	-
Rectal swab			
Incidence of MDR Colonization on rectal swab	28.6 (2)	77.3 (17)	0.02
KPC on rectal swab	100 (1)	52.9 (9)	-
VRE on rectal swab	0	35.3 (6)	-
A.baumanii on rectal swab	0	11.8 (2)	-
Time between ICU entry and first positive rectal swab (median)	10 (8.0-12.0)	11.0 (6.0-21.0)	-

sisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Microflex LT/SH Bruker Daltonik GmbH, Bremen, Germany) equipped with Bruker biotyper 3.1 software. Susceptibility testing for bacteria was performed with determination of minimum inhibitory concentrations (MIC) using the BD Phoenix automated system (Becton Dickinson and Company, Franklin Lakes, New Jersey, USA) and the dedicated panels NMIC-402 and PMIC-88 or Kirby Bauer in case of fastidious bacteria or Sensititre Yeast One (Thermo Fischer Diagnostics B.V., Landsmeer, The Netherlands).

Statistical Analysis

Continuous variables were expressed as a median and interquartile range. Qualitative variables were expressed as their absolute value and percentage. The median values for the continuous variables from both groups were compared using the Mann-Whitney U test. Proportions were compared using the chi-squared test. The crude incidence rate for the bloodstream infections and VAP per 100 person-days of ECMO was calculated and presented with 95% CIs. Cox proportional hazard regression in univariable has been fitted to evaluate the role of SARS-CoV-2 and flu virus on the incidence of infections.

RESULTS

Twenty-nine patients treated with ECMO (22 subjects with SARS-CoV-2 infection (20 males and 2 females) and 7 with flu (4 males and 3 females)) were included in the present study (p=0.04). Their median age was 61 years old for SARS-CoV-2 and 50 for flu (p=0.02). Patient characteristics are summarized in *Table 1*.

Flu viruses were all type A (6 H1N1 and 1 H3N2). Flu was isolated on BAL in 6 (85.7%) of patients and SARS-CoV-2 in 18 (81.8%) of patients.

All patients with flu underwent computerized axial tomography (TC). Three had lung consolidations and four had both ground glass opacity and consolidations, while only 10 patients underwent TC in SARS-CoV-2 (one with lung consolidations and 9 with lung consolidations and ground glass opacity) (*Figure 1*).

Among SARS-CoV-2 infected patients, one patient underwent V-A ECMO for cardiac support and 1 patient was supported prior with V-V ECMO for severe ARDS and after with V-VA ECMO for circulatory shock. All the other patients were supported with V-V ECMO.

All patients were mechanically ventilated during the ECMO period, while renal replacement therapy was introduced in 3 flu and 10 SARS-CoV-2 patients (p=ns).

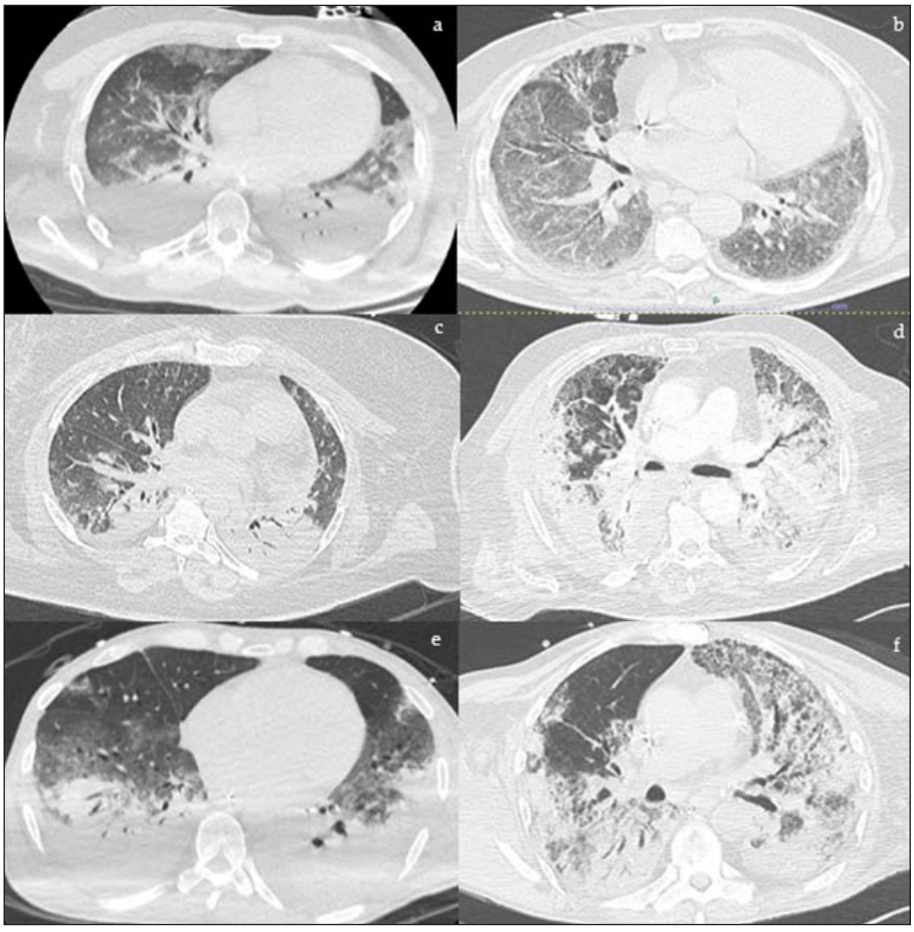

Figure 1 - *Pictures a, c and e are TC-scans from three flu patients. Pictures b, d and f are TC-scans from SARS-CoV-2 patients. In both group we can observe both lung ground glass opacity, multiple consolidations and pleural effusion. As we observed there is no difference in the radiological picture between flu and SARS-CoV-2 infection.*

The median ECMO duration was similar in the two pathologies (12 days in flu and 12.5 days in SARS-CoV-2).

The global infection rate (BSI+VAP) was 5 per 100 patients/days for SARS-CoV-2 patients (95%CI: 3.2-8) and 5.3 per 100 patients/days for flu (95%CI:2.4-11.8) (HR 0.9, 95%CI 0.3-2.2, p=0.8). Median time to bloodstream infection from ECMO initiation was similar (5.5 days for SARS-CoV-2 infection and 7 days for flu infection). Bloodstream infection incidence rate was 2.2 per 100 patients/days for SARS-CoV-2 (95%CI: 1.1-4.4) and 2.65 per 100 patients/days for flu (95%CI: 0.9-8.2) (HR 1.1, 95% 0.3-4, p=0.9).

VAP incidence rate was 3.5 per 100 patient/days for flu (95%CI:1.3-9.4) and 2.9 per 100 patient/days in SARS-CoV-2 infection (95%CI: 1.6-5.4) (OR 0.99, 95% CI 0.3-3.2, p=0.92). Median time to VAP occurrence since intubation was 10.5 days in SARS-CoV-2 and 9.5 days in flu patients.

Pathogens isolated are summarized in *Table 2*. Two patients (28.6%) were colonized on rectal swab among those with flu infection (one patient with *Klebsiella pneumoniae* KPC and one with *Pseudomonas aureginosa* MDR) and seventeen patients (77.3%) with SARS-CoV-2 (52.9% with KPC, 35.3% with VRE, 11.8% with *Acinetobacter baumanii*) (p=0.02). One patient with flu infection developed a VAP and a BSI due to *Klebsiella pneumoniae* KPC at 3 and 6 days, respectively, from positivity on the rectal swab. One patient among those with SARS-CoV-2 infection developed a VAP due to *Klebsiella pneumoniae* KPC 14 days after isolation on rectal swab. Another patient with SARS-CoV-2 infection developed a VAP due to *Klebsiella pneumoniae* KPC 5 days after isolation on rectal swab.

In-hospital mortality was 14.3% for flu (1 out of 7 patients) and 50% for SARS-CoV-2 (p=0.095).

DISCUSSION

Infections represent serious complications in patients undergoing ECMO, occurring in 50% of cases due to the critical illness and the other life supports associated with ECMO (mechanical ventilation and renal replacement therapy) (Grasselli *et al*., 2017).

Secondary infections in severe and critical COVID-19 cases were reported in roughly 40% to 60% of cases, comprehensive of pneumonia, BSIs and urinary tract infections (Zhang *et al*., 2020), and the diagnosis of infections in ICU admitted patients with SARS-CoV-2 was predictive of increased mortality (Bardi *et al*., 2021). Based on this observation it is conceivable to suppose that infections in patients with severe SARS-CoV-2 infection treated with ECMO could be extremely frequent and serious.

In the present paper, the incidence of BSIs in patients with ARDS due to SARS-CoV-2 or flu were overlapping, and consistent with the data (17.2 per 1000 ECMO days) reported in the literature (Allou *et al*., 2019).

VAP incidence was comparable between the two groups of patients. These data are in contrast with those reported by Marcus and Coauthors who observed a higher incidence of co-infections in patients with SARS-CoV-2 compared with patients with H1N1 infection (Marcus *et al*., 2021).

Ventilator-associated pneumonia was diagnosed in 87% of patients and bacteremia was diagnosed in 48% of patients in a large series of subjects with

Table 2 - *Characterization of isolated pathogens.*

			FLU		*Sars-CoV-2*	
	Microorganism	*MDR*	*BAL*	*Blood Cultures*	*BAL*	*Blood Cultures*
Gram-			3	1	13	4
	Klebsiella pneumoniae	KPC	25% (1)	33% (1)	22% (4)	0
	Klebsiella pneumoniae	ESBL	25% (1)	0	0	7% (1)
	Pseudomonas aeruginosa	0	25% (1)	0	11% (2)	13% (2)
	Pseudomonas aeruginosa	CRE			5% (1)	
	Stenotrophomonas maltophila				11% (2)	
	acinetobacter baumanii	CRE	0	0	22% (4)	7% (1)
Gram+			1	2	3	6
	Enterococcus spp	0	0	0	0	27% (4)
	Staphylococcus aureus	PVL	25% (1)	0	11% (2)	0
	Staphylococcus aureus	MRSA	0	0	5% (1)	0
	ConS	0	0	67%(2)	0	13% (2)
Fungi			0	0	2	5
	Aspergillus spp		0	0	11% (2)	0
	Candida spp			0		33% (5)
Tot			4	3	18	15

SARS-CoV-2 infection treated with ECMO; septic shock was the leading cause of death (Schmidt *et al.*, 2020). Similarly, in a cohort of patients treated with ECMO due to H1N1-associated ARDS, the most common cause of death was sepsis and septic shock in more than half of the patients (Pappalardo *et al.*, 2013). Despite the overcrowding of our ICU during the COVID pandemic we did not observe an increased incidence of infections in patients with SARS-CoV-2 compared with flu patients treated with ECMO, as reported by other authors (Marcus *et al.*, 2021).

Survival rates in ECMO patients with COVID vary from 35% to 45% (Dreier *et al.*, 2021; Schmidt *et al.*, 2020; Supady *et al.*, 2021). In the present study, mortality in SARS-CoV-2 infected patients was 45.5%.

A better survival rate was observed in patients with flu, although this observation can be attributed to the low number of patients included.

Staphylococcus aureus represents the most common pathogen associated with ECMO infection in patients with ARDS due to flu infection (Rozencwajg *et al.*, 2018). In the present paper, both Gram-positive and Gram-negative infections were observed for both group on BAL. In SARS-CoV-2, the most common isolated pathogens were *Acinetobacter baumanii* resistant to carbapenems and *Klebsiella pneumoniae* KPC on BAL and *Candida* spp. on bloodstream.

Colonization due to MDR pathogens was higher in SARS-CoV-2 patients, although this was not associated with a major incidence of infections.

In conclusion, limits of our study consist principally of the small population included, and of the retrospective nature of the study. Nevertheless, it may give a good overview of infectious complications of both viral diseases induced by ARDS.

Conflicts of Interest

The authors declare no conflict of interest.

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